REMARKS

Claims 23-26, 29-31, 42-44, 46-49 are pending. Claims 23-25, 31 and 47 have been amended for clarity. Support for claim amendments 23-25 and 31 is found in the claims; support for amendment of claim 47 is found on page 13, line 35; page 59, lines 12-13.

Please cancel claim 45 without disclaimer or prejudice. No new matter is added by way of this amendment. A version showing changes made is attached for the Examiner's convenience. In addition, an appendix of the currently pending claims is also attached hereto. Applicants note that the claims were previously inadvertently misnumbered in the previous response to office action mailed May 1, 2002, excluding claim 46. Applicants have corrected this error and properly numbered the claims.

Rejection under 35 U.S.C § 112, second paragraph

Claims 23-25, 45 and 48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In response, Applicants note that claims 23-25 are rejected for lack of antecedent basis for "said detectable label" in claim 42. Claims 23-25 have been amended for clarity to be dependent from claim 44, not claim 42. This provides proper antecedent basis for the term "said detectable label". Claim 31 has also been amended to be dependent from claim 44 to provide proper antecedent basis for the term "said detectable label". Support is found in the claims.

Claim 45 is rejected for being indefinite for the recitation "said capture probe" "serves" as first ligation probe because the Examiner states that "serves" is a non-descriptive function. Applicants note that claim 45 has been cancelled herein. Accordingly, the rejection is moot.

Claim 47 is rejected as indefinite for the recitation "said capture probe is a protein"

because the Examiner states that it is unclear how the protein hybridizes to a sequence of the ligation product as required in claim 42. Applicants respectfully traverse. Initially Applicants submit that one of skill in the art would be able to understand that the capture probe could be a protein which binds to a nucleic acid sequence. Moreover, Applicants note that the claim has been amended to more clearly describe the invention. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection.

In light of the above amendments and remarks Applicants submit that the claims clearly define the invention. Applicants respectfully request the Examiner to withdraw the rejection.

Rejections under 35 U.S.C § 103

Claims 23-26, 30, 31 and 42-48 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Nikiforov et al. (U.S. Patent No. 5,952,174, issued 14 September 1999) in view of Weisburg et al (U.S. Patent No. 6,110,678, issued 29 August 2000). Claims 23-26, 30, 31 and 43-48 all depend from claim 42 , so the following remarks will focus on claim 42.

Claim 42 is directed to a method of determining the identification of a nucleotide at a detection position in a target sequence. The method includes providing a hybridization complex that includes a target sequence and two primers. The method further includes providing an extension reaction and a ligation reaction to form a ligation product. The method further includes detecting the formed ligation product by hybridizing with microspheres with capture probes that hybridize with a sequence that is contained within the ligation product.

In contrast Nikiforov et al. is directed to a ligase/polymerase mediated method of detecting a nucleotide at a preselected site of a target sequence. The method includes immobilizing a first ligation probe to a solid support that will hybridize to a region of a target sequence, then adding a second ligation probe that will hybridize to a second region of the target.

The first and second probe are separated by a single nucleotide. Following hybridization there are two reactions one of extension of one of the ligation probes and then ligation of both probes. The ligation product is immobilized and detected. Nikiforov does not teach the use of microspheres on the surface of a substrate.

In contrast to the Examiner's characterization, Nikiforov fails to disclose a capture probe that hybridizes to the ligation product.

Weisburg et al. is directed to a method of capturing a target polynucleotide in a sample onto a solid support with an attached immobilized probe by using a capture probe and two different hybridization conditions. The two hybridization conditions control the order of hybridization, where the first hybridization conditions allow hybridization of the capture probe to the target polynucleotide, and the second hybridization conditions allow hybridization of the capture probe to the immobilized probe. Accordingly, what Weisburg calls a "capture probe" appears to be an oligonucleotide that binds both to the target and to an immobilized probe. Weisburg does not teach the use of microspheres are on the surface of a substrate with discrete sites. Finally Weisburg et al. does not teach of a method of determining the identification of a nucleotide at a detection position in a target sequence.

The Examiner states that it would have been obvious to one of ordinary skill in the art to modify the capture of Nikiforov et al. by providing microspheres having capture probes which hybridize to the extension product as taught by Weisburg et al to thereby optimize environmental conditions as suggested by Weisburg et al. for the obvious benefits of maximizing experimental results. Applicants respectfully traverse.

As the Examiner is aware, to establish a prima facie case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally

available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. In addition, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F 2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

In the instant case there is lacking any suggestion or motivation to modify the references or combine reference teachings. As noted briefly above, the Examiner suggests that one of skill in the art would have been motivated to combine references because it was obvious to modify the capture of Nikiforov et al. by providing microspheres having capture probes which hybridize to the extension product as taught by Weisburg et al. to thereby optimize environmental conditions for each method step as suggested by Weisburg et al. for the obvious benefits of maximizing experimental results. However, Applicants submit that this is a legally incorrect determination of motivation. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. In re Mills, 916 F 2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). There is no suggestion in either reference of modifying or combining the references to reach the claims of the present invention. That is, while Weisburg describes in general different conditions, there is nothing that would have motivated one of skill in the art to combine the capture of Nikiforov with the microspheres of Weisburg.

The Examiner's attention in respectfully drawn to In re Lee, 61 USPQ2d 1430 (CA FC 2002). In this case, the Examiner rejected the claims under 35 U.S.C. §103 and stated that the required motivation "would be that the automatic demonstration mode is user friendly and it functions as a tutorial". Id at 1435. The Federal Circuit stated that "deficiencies of the cited references cannot be remedied by the Board's general conclusions about what is "basic knowledge" or "common sense'". The Board's finding must extend to all material facts and must be documented on the record, lest the "haze of so-called expertise" acquire insulation from accountability. "Common knowledge" and "common sense", even if assumed to derived from the agency's expertise, do not substitute for authority when the law requires authority." (citing In re Zurko, 59 USPQ2d 1693 (CA FC 2001); see Lee, 1434-1435). In the present case Applicants submit that the Examiner has failed to point to anything specific in the cited references that would suggest or provide the motivation to combine the references or to modify them. The Examiner has also failed to document on the record what the common knowledge consists of by pointing to specifics and this is legally incorrect under In re Lee.

In this case, the Examiner has essentially used impermissible hindsight and "common sense" to conclude that the combination of these two references would have been motivated by "the obvious benefits of maximizing experimental results". This is legally incorrect under the Federal Circuit's analysis.

Also, in regards to the different conditions of Weisburg as mentioned by the Examiner as a way of optimizing environmental conditions, there is nothing in Nikiforov that requires different conditions. Thus, although different conditions can be used in the presently claimed invention, there is no reason why the skilled artisan would have been motivated to combine Weisburg with Nikiforov from reading this section of Weisburg.

Second, even assuming arguendo that there was motivation to combine references, Applicants respectfully submit that the cited references do not teach all of the claim limitations. The present invention teaches the use of microspheres distributed on a surface. Neither of Nikiforov et al. or Weisburg et al. teach or suggest this aspect of the present invention. Although Weisburg teaches beads, it does not teach distributing the beads on the surface of a substrate. Moreover, Nikiforov et al. does not disclose distributing beads on a substrate with discrete sites.

Since neither Nikiforov et al. or Weisburg et al. teach or suggest the use of a substrate with a surface comprising discrete sites and further comprising microspheres, which are elements of all claims of the present invention, the requirement that the prior art reference (or references when combined) must teach or suggest all the claim limitations has not been met.

In addition, Applicants respectfully submit that neither Weisburg, Nikiforov nor the combination of the two, teach a capture probe that hybridizes to a sequence contained within the ligation product as required in the claims of the present invention. That is, as claimed the capture probe binds a sequence contained in the ligation product. However, in Nikiforov the immobilized primer binds the target and forms the ligation product which is already immobilized through the initial immobilized primer. Moreover, there is no ligation product formed in Weisburg to which a capture probe could bind. Again, the requirement that the prior art reference (or references when combined) must teach or suggest all the claim limitations has not been met. Applicants submit that a *prima facie* case of obviousness has not been satisfied. Applicants respectfully request that the Examiner withdraw the rejection.

Claims 29 and 49 are rejected under 35 U.S.C.§ 103(a) as being unpatentable over Nikiforov et al. (U.S. Patent No.: 5,952,174, issued 14 September 1999) in view of Weisburg et

al. (U.S. Patent No. 6,110,678, issued 29 August 2000) as applied to claim 42 and further in view of Walt et al. (U.S. Patent No.: Patent No. 6,327,410, filed 11 September 1998).

The distinctions between Nikiforovet al. and Weisburg et al. and the present invention are discussed above and incorporated at this point by reference.

Walt et al. is directed to, among other things, the use of microspheres comprising oligonucleotides attached to microspheres to detect the presence or absence of nucleic acid sequences. Walt et al. is silent with respect to teaching the combination of ligation and extension reactions (Genetic Bit Analysis™) or any polymorphism detection assays.

The Examiner states that it would have been obvious to apply the fiber optic substrate of Walt et al. to the substrate of Nikiforov et al. and Weisburg et al. for the obvious benefits of detecting an extremely high number of targets. Applicants respectfully traverse.

Obviousness is tested by what the combined teachings of the references would have suggested to those of ordinary skill in the art. It cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. And teachings of references can be combined *only* if there is some suggestion or incentive to do so. *In reFine, 5* USPQ2d *1596, 1599* (CAFC 1988) (quoting *In re Keller,* 208 USPQ 871,881 (CCPA 1981) *and ACS Hosp. Sys. v. Mont efiore Hosp.,* 221 USPQ 929, 933 (CAFC 1984)).

As noted previously there must be some motivation or suggestion in the prior art to modify or combine reference teachings to arrive at the claimed invention. Here, there is lacking any suggestion or motivation in the prior art to arrive at the use of microspheres on the surface of a substrate for determining the identity of a nucleotide at a detection position through the combination of extension and ligation reactions, elements of all claims of the present invention.

As noted above, there is no motivation and the Examiner has failed to point to anything specific in the cited references that would suggest the motivation to combine Nikiforov with Weisburg and Walt to reach the claims of the present invention.

As the Examiner is aware, "obvious to try" is not the standard. The Examiner makes a very general statement of "expected benefit". As noted above in the In re Lee case, "common sense" is not an adequate motivation to combine. It is improper to use an obvious to try approach or to cite to only general guidance as to the particular form of the claimed invention or how to achieve it. See In re O'Farrell, 853 F. 2d 894,903, 7 USPQ2d 1673,1681 (Fed. Cir. 1988). Accordingly the rejection is improper and the Applicants respectfully request the withdrawal of the rejection.

Even assuming arguendo, that there was motivation, not all claim elements are present in the cited prior art references because none of the references individually or in combination teach a capture probe that hybridizes to a sequence contained within the ligation product, an element of all claims of the present invention. Weisburg et al. uses a probe that binds to the target sequence and forms a part of the ligation product, but it does not bind to a sequence contained within the ligation product. Nikiforv discloses the use of a immobilized primer that binds the capture probe. However, neither probe binds to a sequence contained within the ligation product. Walt et al. as mentioned above is silent with respect to teaching the combination of ligation and extension reactions (Genetic Bit Analysis™) or any polymorphism detetction assays.

Accordingly, Applicants respectfully submit that the Examiner has failed to set forth a *prima facie* case of obviousness because the motivation or suggestion to make the combination that reaches the claimed invention is not found in the prior art. In addition not all claim elements

are present in the cited prior art. Therefore, Applicants respectfully request that the rejection be withdrawn.

In response to the Examiner's points regarding the previously submitted secondary considerations of commercial success, Applicants maintain that the secondary consideration of commercial acquiescence compel a finding of nonobviousness.

The Supreme Court of the United States has stated that "such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origins of the subject matter sought to be patented." Graham v. John Deere Co., 148 USPQ 459 (1966). The Federal Circuit has emphatically and repeatedly held that objective evidence of nonobviousness must be taken into account always and not just when the decision maker is in doubt (see, for example, Hybridtech Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81 (Fed. Cir. 1986); Bausch & Lomb, Inc. v. Barnes Hindes, Inc., 230 USPQ 416 (Fed. Cir. 1986); Jones v. Hardy, 220 USPQ 1021 (Fed. Cir. 1984)).

The Examiner states that the Applicants have not clearly established a nexus between the claimed invention and commercial success, and repeatedly suggests that any commercial success is the result of advertising and promotion.

As a preliminary matter, the Examiner is respectfully reminded that the presence of advertising and marketing does not preclude a finding of both the required nexus and commercial success. As the Federal Circuit stated in Hybritech Inc. v. Monoclonal Antibodies, Inc., the evidence of advertising by the patentee did not show an absence of nexus between commercial success and the merits of the claimed invention because "this is not the kind of merchandise that can be sold by advertising hyperbole"; see 231 USPQ 81, 92 (Fed. Cir. 1986). In this regard, Applicant points out that, similar to the sophisticated diagnostic kits of the Hybritech case,

genotyping services of patient samples using state of the art technology is similarly "not the kind of merchandise that can be sold by advertising hyperbole". In addition, the sophistication of Illumina's partners leads to a finding of commercial success; GlaxoSmithKline is the world's leading research-based pharmaceutical firm and has a leading position in genomics/genetics and in the use of new drug discovery technologies; John Hopkins Medical University, University of California at San Diego and Boston University Medical Center are similarly world renowned institutes, unlikely to be wooed by mere advertising. As in the Hybritech case, the advertising primarily serves to make persons in the industry (such as hospitals, doctors and clinical laboratories) aware of the available product. See also Ex parte Parsons, 229 USPQ 635, 636 (Bd. Pat App. and Int'f 1986) "Advertising is not a factor; the buyers are technically sophisticated".

In further support of this position, the statement of Oxagen's CEO is telling, as showing that Illumina's BeadArray™ platform has clear technical merits which serve as the basis of their choice to use the platform.

The Examiner further states that the Declaration does not provide evidence that the products sold correspond to the claimed invention. As outlined in the Declaration, the "products sold" are genotyping assays; the customer sends in samples to be genotyped, and Illumina runs the assays internally. In paragraph 5 of his Declaration, Dr. Stuelpnagel states that Illumina conducts genotyping assays. The method (outlined in paragraph 5) is exactly what is claimed in claim 42, specifically, ligation and extension assays are currently run.

The patentee's proof may consist of evidence that the patentee and its competitors consistently used the patented feature. Se Hughes Tool Co. v. Dresser Industries Inc., 816 F.2d 1549, 2 USPQ2d 1396 (Fed. Cir. 1987), *cert denied*, 484 U.S. 914 (1987). Continued use of the patented feature while other features were not copied gives rise to an inference that there is a

nexus between the patented feature and the commercial success. Hughes Tool Co., 816 F. 2d at 1556, 2 USPQ2d at 1402.

Here the fact that the features of Applicant's claimed invention, as outlined above and in the claims, are in continuous use by Applicant and sophisticated institutions, gives rise to an inference that there is a nexus between the patented feature and the commercial success.

When the patentee has presented a prima facie case of nexus, the burden of coming forward with evidence in rebuttal shifts to the challenger. It is thus the task of the challenger to adduce evidence to show that the commercial success was due to extraneous factors other than the patented invention. Demarco Corp. v. F. Von Langsdorff Licensing Ltd., F 2d at 1393, 7 USPQ2d 1222,1226. Here the Examiner has failed to adduce any evidence that the commercial success of Applicant's invention was due to extraneous factors other that the features of the claimed invention. Accordingly the rejection is improper. Applicants respectfully request the withdrawal of the rejection.

In conclusion, neither Nikiforov et al., Weisburg et al. or Walt et al. or their combination teach or suggest the use of microspheres on the surface of a substrate for determining single nucleotide polymorphisms through the combination of extension and ligation reaction as claimed. In addition the strong factual evidence of commercial acquiescence as a secondary consideration of nonobviousness as previously provided in response to office action mailed May 1, 2002, necessitate a finding of nonobviousness.

The Applicants respectfully submit that the rejection of claims based on 35 U.S.C § 103 obviousness is improper and respectfully requests the withdrawal of the rejections.

CONCLUSION

Applicants submit that the claims are now in condition for allowance and early notification to that effect is respectfully solicited. If the Examiner feels there are any unresolved issues, the Examiner is encouraged to contact the undersigned at 415-781-1989.

Respectfully submitted,

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VERSION SHOWING CHANGES MADE

23. (Amended) The method according to claim [42] 44, wherein said detectable label comprises a fluorophore.

24. (Amended) The method according to claim [42] 44, wherein said detectable label comprises biotin.

25. (Amended) The method according to claim [42] 44, wherein said detectable label comprises imine-biotin.

31. (Amended) The method according to claim [42] 44, wherein said detectable label is a fluorophore.

45. (cancel)

47. (Amended) The method according to claim 42, wherein said capture probe is a protein, wherein said protein binds to said sequence contained within said ligation product.